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(57) Abstract

A rapid release tablet comprising an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof. The active ingredient has a mean particle size of ≤ 10 μm. The tablet comprises alginic acid or a pharmaceutically acceptable salt thereof in an amount of 1.5 - 6.0 % by weight and a superdisintegrant in an amount of at least 6 % by weight.

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RAPID RELEASE TABLET COMPRISING TOLFENAMIC ACID OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

This invention relates to to a tablet comprising an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof which is capable of rapid release of the active ingredient. In addition the invention relates to a method of preparing such tablet.

Tolfenamic acid, N-(2-methyl-3-chlorophenyl)-anthranilic acid, and salts thereof are known compounds having antiinflammatory and analgesic activity. The compounds and their aforementioned activities as well as a method of preparing the compounds have been described in DK patent no. 116 061.

During the treatment of patients suffering from rheumatic diseases with tolfenamic acid preparations some patients noticed a reduced occurrence of migraine attacks, and tolfenamic acid is now being marketed both as antiinflammatory and analgesic agent, particularly for the treatment of rheumatic diseases and dysmenorrhoea, and as anti-migraine agent (prophylactic as well as curative).

The tolfenamic acid preparations were originally formulated as capsules consisting of a hard gelatine capsule shell containing a loose powder of the tolfenamic acid in admixture with usual tablet and capsule fillers, the powder being made available for dissolution in the gastro-intestinal tract, when the gelatine capsule has been dissolved.

The capsule formulation was chosen because of difficulties in preparing a tablet containing a therapeutic dose and still being of a reasonable size, as a tablet of a size which could be easily swallowed by a

patient, turned out to be very difficult to disintegrate.

Later efforts resulted in the development of tablets being capable of providing a bioavailability of the tolfenamic acid corresponding to that obtained by the tolfenamic acid capsules. Furthermore the maximum plasma concentration was found to be somewhat higher for the tablet formulation than for the capsule formulation. However, T_{max}, the time at which the maximum plasma concentration is obtained, was essentially unchanged.

The potential of tolfenamic acid of curing a migraine attack has accentuated the desire of obtaining a small tablet which is capable of providing a high plasma concentration of tolfenamic acid within a short time.

As a result of extensive research aiming at attaining this object, a tablet having these characteristics has now been developed. Thus a tablet has been provided, which is capable of providing a maximum plasma concentration of tolfenamic acid being almost twofold of that obtained with the capsule formulation (mean values of 5.60 µg/ml and 2.95 µg/ml, respectively, in a cross-over test carried out on 12 test persons), and furthermore within about half the time after administration (T_{max} median values of 1.0 hours and 1.8 hours, respectively). As a further essential point, the mean plasma concentration reached half an hour after administration of the tablet according to the invention has been found to be more than twofold of that obtained by the known tablet, 2.60 µg/ml and 1.18 µg/ml, respectively. Thus a therapeutic level of tolfenamic acid is reached much faster by administration of the tablet according to the invention than by administration of the known tablet, among other things making the tablet

according to the invention particularly suited for acute treatment of a migraine attack.

These surprising results are based on a selection of a particular combination of tablet formulation aids and a particular particle size of the active ingredient.

Accordingly the invention provides a tablet comprising an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof, said active ingredient having a mean particle size of ≤ 10 μm, and said tablet furthermore comprising alginic acid or a pharmaceutically acceptable salt thereof in an amount of 1.5 - 6.0 % by weight and a superdisintegrant in an amount of at least 6 % by weight.

The designation superdisintegrant refers to a group of disintegration agents being well-known to a person skilled in the art. Generally speaking, superdisintegrants are disintegration agents which can be used in a fractional amount of normal disintegrants to obtain the same effect. According to product information provided by the manufacturers of superdisintegrants, the superdisintegrants should be used in amounts of 1 - 8 % with amounts of about 2% to about 4 % being indicated as optimal. Thus the amounts of superdisintegrant used according to the invention are higher than the amounts generally used.

Cross-linked polyvinylpyrrolidones, particularly crospovidone, modified starches, particularly sodium starch glycolate, Starch 1500, modified celluloses, particularly croscarmellose sodium (cross-linked sodium carboxymethylcellulose), LHPC (Low substituted hydroxypropylcellulose) and Veegum are examples of preferred superdisintegrants for use in the tablet according to the invention.

Croscarmellose sodium is f.inst. commercialized under the trade name Ac-Di-Sol and sodium starch glycolate under the trade names Primojel and Explotab. Kollidon CL and Polyplasdone XL are commercial cross-linked PVP products.

According to the invention, the superdisintegrant will be present in the tablet in an amount of at least 6 % by weight, such as in an amount at least 8 % by weight, particularly in an amount of at least 10 % by weight and preferably in an amount of at least 12 % by weight. The superdisintegrant may be a single superdisintegrant or a combination of superdisintegrants and will normally be used in combination with one or more common disintegrants, such as starch, f. inst. corn starch.

There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. However, normally the amount of superdisintegrant will not exceed 25 % by weight. From a cost point of view, the amount of superdisintegrant will preferably not exceed 15 -20 % by weight as normally no particular benefits will be achieved beyond this range.

The superdisintegrant may be present as an extragranular and/or as an intragranular disintegration agent. According to one embodiment of the invention the superdisintegrant is present both as an intragranular disintegration agent and as an extragranular disintegration agent. Although the superdisintegrant may be present solely as an intragranular disintegration agent, it will in most cases be present as an extragranular disintegration agent, either solely as an extragranular disintegration agent or in combination with an intragranular disintegration agent as mentioned above.

The particle size of the active ingredient can be obtained in different ways, such as by milling or micronizing. The mean particle size can f.inst. be determined by the so-called Malvern technique, f. inst. using a Malvern Instrument of the type M6.10.

Typically milling results in a mean particle size in the upper half of the range from zero up to 10 μm whereas micronizing results in a mean particle size in the lower half of said range.

In a preferred embodiment of the invention, the mean particle size of the active ingredient is ≤ 8μm.

A typical mean particle size of tolfenamic acid for use as active ingredient in the tablet according to the invention as obtained by milling is in the range from 5 - 7 μm with a specific surface area in the range from 1.0 - 1.8 m^2/cm^3, particularly in the range from 1.1 - 1.7 m^2/cm^3, as determined by the above mentioned Malvern technique.

A typical mean particle size of tolfenamic acid for use as active ingredient in the tablet according to the invention as obtained by micronizing is in the range from 1.5 - 2.5 μm with a specific surface area in the range from 2.5 - 3.5 m^2/cm^3, as determined by the Malvern technique.

Generally the specific surface area of the active ingredient will be in the range from 1.0 - 4.0 m^2/cm^3.

As the micronizing process is more expensive than milling and no particular advantages seem to be obtained by a micronized product compared to a milled product, the latter is normally preferred from a cost point of view.

The very hydrophobic nature of tolfenamic acid necessitates the use of an agent being capable of reducing the hydrophobicity of the particles, and alginic acid and pharmaceutically acceptable salts

thereof have been found particularly suited for that purpose. Thus a dissolution of 86 % of the tolfenamic acid included in a tablet as active ingredient has been obtained within 3 minutes by use of alginic acid as granulation agent compared to 32 % and 47 %, respectively, by use of the conventional granulation agents, polyvinylpyrrolidone and gelatine.

Similarly milling or micronizing results in an increase of the dissolution within 3 minutes by about two thirds compared to an unmilled product. Thus also the particle size appears to be of importance.

Finally the use of a superdisintegrant in an amount of at least 6 % by weight has turned out to be an important feature for obtaining the desired rapid release of the active ingredient.

The alginic acid or pharmaceutically acceptable salt thereof is generally included in an amount of 1.5 - 6.0 % by weight and preferably in an amount of 2.5 - 5.0 % by weight.

Alkali metal salts, such as the sodium and potassium salts, are examples of pharmaceutically acceptable salts of alginic acid which may be used according to the invention.

In a preferred embodiment of the invention the alginic acid or pharmaceutically acceptable salt thereof is used as a granulation agent in the preparation of the tablet.

A presently preferred embodiment of the invention relates to a tablet comprising from 40 - 70 % by weight of the active ingredient, from 2.5 - 5.0 % by weight of alginic acid or a pharmaceutically acceptable salt thereof, from 6 - 10 % by weight of intragranular sodium starch glycolate, from 3 - 5 % by weight of extragranular sodium starch glycolate and from 1 - 3 % by weight of extragranular croscarmellose sodium, the

remainder up to 100 % by weight consisting of conventional tablet formulation aids, such as fillers, binding agents, disintegrants, lubricants, etc.

In a further aspect of the invention a method of preparing a tablet as indicated above is provided, said method comprising the following steps:

a) blending an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof having a mean particle size of ≤ 10 μm with a disintegration agent and optionally other intragranular tablet formulation aids,

b) kneading the resulting blend with a solution or dispersion of alginic acid or a pharmaceutically acceptable salt thereof to form a moist homogeneous mass, the alginic acid or pharmaceutically acceptable salt thereof being used in an amount to give a concentration thereof in the resulting tablet of 1.5 - 6.0 % by weight, and granulating the moist homogeneous mass,

c) drying the obtained granules, optionally after blending with a filler and/or other tablet formulation aids,

d) blending the dried granules with a disintegration agent and optionally other extragranular tablet formulation aids, and

e) compressing the resulting blend into a tablet,

with the proviso that the disintegration agent used in step a) and/or step d) comprises one or more superdisintegrants in a total amount to give a concentration of superdisintegrant in the resulting tablet of at least 6 % by weight.

The invention also relates to the use of tolfenamic acid or a pharmaceutically acceptable salt thereof having a mean particle size of ≤ 10 μm in combination

with alginic acid or a pharmaceutically acceptable salt thereof and a superdisintegrant for the preparation of a tablet for treatment of pain, inflammation, migraine, dysmenorrhoea and fever, particularly for acute treatment thereof, the alginic acid or pharmaceutically acceptable salt thereof and the superdisintegrant being used in amounts of 1.5 - 6.0 % by weight and at least 6 % by weight, respectively.

The tablets according to the invention comprising tolfenamic acid or a pharmaceutically acceptable salt thereof as active ingredient will usually be administered in a daily dose corresponding to 200 - 600 mg of tolfenamic acid with a unit dose of 200 mg per tablet. Using the formulation according to the invention, a rapid release tablet containing such unit dose of 200 mg can be made with a total weight as low as about 350 -375 mg. If desired, the tablets according to the invention can also be prepared to contain multiples of such unit doses, in which case the tablets will be provided with means such as notches for easy division into suitable parts. F. inst. tablets containing a double dose and being provided with a notch for easy division into two halves can be prepared. Also tablets containing a single dose can be notched for easy division, if desired. Furthermore the tablets can be provided with identification codes.

In a preferred aspect, the invention provides a tablet comprising a unit dose of tolfenamic acid or a pharmaceutically acceptable salt thereof, of about 200 mg tolfenamic acid, or a multiple of such unit dose, and having a total weight of 350 - 400 mg per unit dose, preferably about 375 mg per unit dose.

As a further preferred aspect, the invention provides a tablet being capable of providing a mean plasma

concentration of tolfenamic acid of about 2.00 µg/ml within half an hour after administration.

In the drawings

Figure 1 illustrates mean plasma concentration curves for tolfenamic acid tablets according to the invention and tolfenamic acid capsules and tablets according to the prior art, and

Figure 2 dissolution curves for the same tolfenamic acid preparations.

In the following the tablet of the invention and its method of preparation will be further illustrated by examples which should not be regarded as limiting.

Example 1.

Rapid release tablets, each containing 200 mg of tolfenamic acid as active ingredient, were prepared using the following ingredients and procedure.

	Ingredients		Amount
I.	Tolfenamic acid, milled to a mean particle size of about 5.7 µm		1000 g
-	Amyl. maidis (corn starch)		320 -
-	Sodium starch glycolate		150 -
II.	Alginic acid		60 g
-	Aq. purificata 100 °C		500 -
-	Aq. purificata 10 - 12 °C		750 -
III.	Cellulose, microcrystalline	ad	1530 g
IV.	Cellulose, microcrystalline		120 g
-	Polyethylene glycol 6000		75 -
-	Croscarmellose sodium		35 -
-	Silicium dioxide		10 -
-	Sodium starch glycolate		75 -
-	Sodium stearyl fumarate		15 -

I is blended in a suitable intensive blender for 60 sec. after which the prepared solution II is added and worked into I until adequate wetting.

The wet mass of I + II is passed through a screen having a mesh width of 2.5 mm (8 mesh). Then the prepared granules are dried to a weight of 1480 - 1530 g in a suitable fluidizer and supplemented to 1530 g with III as necessary.

After drying the granules are screened on a screen having a mesh width of 1.5 mm (12 mesh).

The ingredients under IV are screened on a screen having a mesh width of 0.15 mm (100 mesh) and then added to the dry-screened granules in a suitable mixing apparatus for final mixing.

The resulting granules are formed into tablets of a gross weight of 372 mg and containing 200 mg of tolfenamic acid each, using oval matrices of 7 x 14 mm optionally provided with a dividing notch and an identification code on one of its faces.

The above amounts are adequate for the preparation of 5000 tablets.

Example 2

Using the same procedure as described in example 1 tablets of the following content were prepared.

Tolfenamic acid, milled to a mean particle size of about 6.2 µm	200	
Amylum maidis	64	-
Sodium starch glycolate	22.5	-
Polyethylene glycol	15	-
Alginic acid	12	-
Cellulose, microcrystalline	24	-
Croscarmellose sodium A	5.25	-
Silicium dioxide	2	-

Sodium starch glycolate		11.25	-
Sodium stearyl fumarate		3	-

Comparative example 1

Preparation of tolfenamic acid capsules according to the prior art.

Capsules, each containing 200 mg of tolfenamic acid as active ingredient, were prepared using the following ingredients and procedure.

	Ingredients		Amount	
I.	Tolfenamic acid, unmilled		1000	g
-	Lactose		403.5	-
-	Amyl. maidis		167.5	-
II.	Polyvinylpyrrolidone		16.5	g
-	Ethanol		160.0	-
-	Aq. purificata		200.0	-
III.	Amyl. maidis	ad	1587.5	g
IV.	Polyethylene glycol 6000		75.0	g
-	Talc		87.5	-

I is blended in a suitable intensive blender for 60 sec. after which the prepared solution II is added and worked into I until adequate wetting.

The wet mass of I + II is passed through a screen having a mesh width of 2.5 mm (8 mesh). Then the prepared granules are dried to a weight of 1550 - 1587.5 g in a suitable fluidizer and supplemented to 1587.5 g with III as necessary.

After drying the granules are screened on a screen having a mesh width of 1.0 mm (18 mesh).

The ingredients under IV are screened on a screen having a mesh width of 0.15 mm (100 mesh) and then added to the dry-screened granules in a suitable mixing apparatus for final mixing.

The resulting granules are filled into hard gelatine capsules of size 2 in an amount of 350 mg/capsule corresponding to 200 mg tolfenamic acid/capsule, using a suitable capsule filling apparatus.

The above amounts are adequate for the preparation of 5000 capsules.

Comparative example 2.

Preparation of tolfenamic acid tablets according to the prior art.

Tablets, each containing 200 mg of tolfenamic acid as active ingredient, were prepared using the following ingredients and procedure.

	Ingredients		Amount
I.	Tolfenamic acid, unmilled		1000 g
-	Lactose		250 -
-	Amyl. maidis		300 -
II.	Polyvinylpyrrolidone		75 g
-	Ethanol		80 -
-	Aq. purificata		100 -
III.	Amyl. maidis	ad	1625 g
IV.	Cellulose, microcrystalline		100 g
-	Silicium dioxide		10 -
-	Croscarmellose sodium		35 -
-	Sodium stearyl fumarate		15 -
-	Polyethylene glycol 6000		75 -

I is blended in a suitable intensive blender for 60 sec. after which the prepared solution II is added and worked into I until adequate wetting.

The wet mass of I + II is passed through a screen having a mesh width of 2.5 mm (8 mesh). Then the prepared granules are dried to a weight of 1600 - 1625 g

in a suitable fluidizer and supplemented to 1625 g with III as necessary.

After drying the granules are screened on a screen having a mesh width of 1.5 mm (12 mesh).

The ingredients under IV are screened on a screen having a mesh width of 0.15 mm (100 mesh) and then added to the dry-screened granules in a suitable mixing apparatus for final mixing.

The resulting granules are formed into tablets of a gross weight of 372 mg and containing 200 mg of tolfenamic acid each, using oval matrices of 7 x 14 mm optionally provided with a dividing notch and an identification code on one of its faces.

The above amounts are adequate for the preparation of 5000 tablets.

Comparative example 3.

Bioavailability studies.

Tolfenamic acid tablets according to the invention, prepared as described in example 1 and tolfenamic acid capsules prepared as described in comparative example 1 were compared as to bioavailability of tolfenamic acid after oral administration, in a randomized single dose cross-over study carried out on 12 healthy volunteers.

Blood samples were collected after 1/4, 1/2, 1, 1 1/2, 2, 3, 4, 6 and 8 hours and the plasma concentration of tolfenamic acid in μg/ml was determined. The individual results are listed in tables Ia and IIa below, together with the mean and SEM values of the plasma concentrations obtained after 1/4, 1/2, 1 hour etc.

Table Ia

Tolfenamic acid tablets 200 mg, according to the invention.

Subject No. Time (h)	Plasma concentration, µg/ml								
	¼	½	1	1½	2	3	4	6	8
1	<0.05	0.07	0.44	4.68	6.57	1.98	0.68	0.21	0.12
2	3.16	5.21	6.39	4.18	2.48	1.51	0.54	0.52	0.20
3	<0.05	3.08	5.97	4.61	3.05	0.92	0.93	0.57	0.14
4	0.00	0.76	4.49	4.43	2.00	0.78	0.28	0.14	0.11
5	0.26	0.74	3.77	7.10	5.98	2.89	1.65	0.42	0.33
6	1.91	5.79	4.21	3.08	2.15	1.06	0.64	0.17	0.08
7	0.14	2.56	5.35	4.86	3.21	1.80	0.64	0.33	0.17
8	0.19	4.30	4.26	1.70	0.78	0.60	0.24	0.32	0.15
9	0.00	0.09	0.23	3.32	5.99	2.49	1.13	0.18	0.20
10	<0.05	1.92	2.65	2.01	2.92	0.90	0.29	0.12	0.11
11	<0.05	1.92	4.30	6.52	7.63	4.36	1.87	0.48	0.45
12	0.95	4.70	4.44	2.96	2.09	1.06	0.41	0.32	0.12
Mean	0.55	2.60	3.88	4.12	3.74	1.70	0.78	0.32	0.18
SEM	0.29	0.58	0.55	0.47	0.64	0.32	0.15	0.04	0.03

Table IIa

Tolfenamic acid Capsules 200 mg.

Subject No. Time (h)	Plasma concentration, µg/ml								
	¼	½	1	1½	2	3	4	6	8
1	0.00	0.00	1.88	3.66	3.88	2.12	0.95	0.23	0.17
2	0.22	1.27	3.47	4.16	4.24	2.36	0.94	0.22	0.25
3	<0.05	0.14	1.63	5.35	5.04	1.82	0.78	0.14	0.07
4	0.00	0.00	0.19	0.63	0.83	1.42	1.78	0.43	0.26
5	0.00	0.32	3.30	3.94	3.54	2.16	1.48	0.38	0.21
6	0.00	0.13	2.47	3.45	3.06	1.61	0.85	0.55	0.20
7	0.00	0.70	2.43	2.50	2.00	2.03	0.97	0.32	0.15
8	0.00	0.06	0.32	1.17	1.46	2.06	0.89	0.38	0.19
9	<0.05	0.18	1.69	2.13	2.02	1.42	1.05	0.72	0.31
10	<0.05	0.86	1.69	1.88	2.68	1.27	0.56	0.15	0.15
11	0.00	0.00	0.00	<0.05	0.09	0.32	0.57	1.19	1.58
12	0.00	0.53	1.84	1.70	1.76	1.81	0.70	0.61	0.21
Mean	0.02	0.35	1.74	2.55	2.55	1.70	0.96	0.44	0.31
SEM	0.02	0.12	0.32	0.46	0.42	0.16	0.10	0.09	0.12

In table IIIa below the maximum plasma concentration, C_{max}, and the area under the plasma concentration curve, $AUC_{0-\infty}$, for each test person are listed together with the mean and SEM values.

Table IIIa

Subject No.	Tolfenamic acid tablet, 200 mg, according to the invention		Tolfenamic acid capsule, 200 mg, prior art	
	C_{max} µg/ml	$AUC_{0-\infty}$ (µg/ml)h	C_{max} µg/ml	$AUC_{0-\infty}$ (µg/ml)h
1	6.57	11.61	3.88	11.12
2	6.39	14.01	4.24	13.53
3	5.97	12.65	5.35	10.61
4	4.49	8.14	1.78	7.06
5	7.10	17.60	3.94	12.53
6	5.79	10.37	3.45	10.43
7	5.35	12.45	2.50	9.16
8	4.30	7.65	2.06	6.97
9	5.99	11.93	2.13	10.25
10	2.92	7.21	2.68	7.02
11	7.63	21.69	1.58	16.56
12	4.70	9.97	1.84	8.18
Mean	5.60	12.11	2.95	10.29
SEM	0.38	1.21	0.35	0.84

As will be seen, the tablet according to the invention results in a maximum plasma concentration being almost twofold of that obtained by the capsule formulation (5.60 µg/ml vs. 2.95 µg/ml). In addition, the total area under the plasma concentration curve appears to be larger for the tablet according to the invention than for the capsule preparation, indicating

that the tolfenamic acid is utilized more efficiently in the tablet according to the invention than in the capsule formulation.

As a further important feature, the maximum plasma concentration is obtained in a much shorter time (T_{max} median values of 1.0 hours and 1.8 hours, respectively), as will appear from table IVa below wherein the time, T_{max}, for each test person to reach C_{max} is listed together with the median value.

Table IVa

Subject No.	Tolfenamic acid tablet, 200 mg, according to the invention, T_{max} (h)	Tolfenamic acid capsule, 200 mg, prior art, T_{max} (h)
1	2.0	2.0
2	1.0	2.0
3	1.0	1.5
4	1.0	4.0
5	1.5	1.5
6	0.5	1.5
7	1.0	1.5
8	0.5	3.0
9	2.0	1.5
10	2.0	2.0
11	2.0	8.0
12	0,5	1.0
Median	1.0	1.8

In a corresponding randomized single dose cross-over study carried out on 12 healthy volunteers, tolfenamic acid tablets according to the prior art

prepared as described in comparative example 2 was compared to the capsule formulation prepared in comparative example 1 with the results indicated in tables Ib - IVb below, table Ib corresponding to the above table Ia, etc.

Table Ib

Tolfenamic acid tablets 200 mg, prior art.

Subject No. Time (h)	Plasma concentration, µg/ml						
	½	1	1½	2	3	4	8
1	0.58	3.09	4.12	2.48	1.44	0.59	0.24
2	2.80	6.56	4.32	3.08	1.11	0.85	0.19
3	3.26	5.79	4.48	2.98	1.20	0.49	0.29
4	2.37	3.67	3.64	2.25	1.18	1.30	0.39
5	0.77	1.94	2.71	2.55	2.64	1.52	0.54
6	0.09	2.27	3.20	2.28	1.50	0.79	0.19
7	0.42	1.87	2.04	1.58	1.29	0.45	0.18
8	0.80	3.22	3.36	2.92	1.77	1.15	0.27
9	1.11	4.30	3.25	1.85	0.80	0.45	0.25
10	0.19	1.58	2.89	2.95	2.76	2.19	0.61
11	1.17	3.01	3.75	2.86	1.66	1.30	0.26
12	0.57	1.23	1.76	3.30	1.17	0.70	0.60
Mean	1.18	3.21	3.29	2.59	1.55	0.98	0.33
SEM	0.30	0.48	0.24	0.15	0.17	0.15	0.05

Table IIb

Tolfenamic acid Capsules 200 mg.

Subject No. Time (h)	Plasma concentration, µg/ml						
	½	1	1½	2	3	4	8
1	0.07	0.29	2.04	2.31	1.66	1.67	0.36
2	3.22	4.68	3.55	2.21	0.72	0.46	0.17
3	0.22	2.31	2.18	2.15	1.46	1.39	0.35
4	1.19	3.21	2.49	2.08	1.57	1.03	0.45
5	0.00	1.50	1.66	1.64	1.91	1.12	0.36
6	0.39	1.23	1.61	1.29	1.38	0.97	0.19
7	2.09	2.35	1.58	0.98	0.57	0.49	0.33
8	0.25	1.83	2.57	2.28	1.65	0.98	0.38
9	0.00	0.28	1.00	1.08	1.16	0.95	0.86
10	0.42	0.99	1.45	2.13	2.34	2.76	0.55
11	0.47	1.72	2.05	1.88	1.24	1.07	0.27
12	0.12	2.79	3.50	3.36	1.74	1.31	0.51
Mean	0.70	1.93	2.14	1.95	1.45	1.18	0.40
SEM	0.29	0.36	0.23	0.19	0.14	0.17	0.05

Table IIIb

Subject No.	Tolfenamic acid tablet, 200 mg, prior art		Tolfenamic acid capsule, 200 mg, prior art	
	Cmax (µg/ml)	AUC 0-26h (µg/ml)h	Cmax (µg/ml)	AUC 0-26h (µg/ml)h
1	4.12	11.36	2.31	13.36
2	6.56	14.86	4.68	11.73
3	5.79	15.12	2.31	13.39
4	3.67	15.04	3.21	14.06
5	2.71	16.89	1.91	12.19
6	3.20	9.87	1.61	8.58
7	2.04	7.58	2.35	8.84
8	3.36	13.69	2.57	12.59
9	4.30	10.84	1.16	14.36
10	2.96	19.25	2.76	18.45
11	3.75	13.82	2.05	10.55
12	3.30	15.06	3.50	16.66
Mean	3.81	13.62	2.54	12.90
SEM	0.37	0.93	0.27	0.83

Table IVb

Subject No.	Tolfenamic acid tablet, 200 mg, prior art, T_{max} (h)	Tolfenamic acid capsule, 200 mg, prior art, T_{max} (h)
1	1.5	2.0
2	1.0	1.0
3	1.0	1.0
4	1.0	1.0
5	1.5	3.0
6	1.5	1.5
7	1.5	1.0
8	1.5	1.5
9	1.0	3.0
10	2.0	4.0
11	1.5	1.5
12	2.0	1.5
Median	1.5	1.5

Although the tablet according to the prior art results in a somewhat higher maximum plasma concentration than the capsule preparation, 3.81 µg/ml vs. 2.54 µg/ml, cf. table IIIb, the increase is much smaller than that obtained by the tablet according to the invention, resulting in an increase from 2.95 µg/ml to 5.60 µg/ml, as indicated in the above table IIIa. Furthermore, the prior art tablet has the same T_{max} median value as the capsule preparation.

Thus the tolfenamic acid tablet according to the invention results in a substantively increased maximum plasma concentration being obtained in a substantively reduced period of time, not only compared to the known capsule preparation but also compared to the known

tolfenamic acid tablet. Furthermore the tablet according to the invention results in a higher total area under the plasma concentration curve that the two other preparations meaning that a higher utilization of the active ingredient can be achieved.

The above results are further illustrated in Figure 1 wherein mean plasma concentration curves for the three preparations are shown.

Dissolution tests

The dissolution tests are carried out according to Ph.Eur. V.5.4 using a paddle apparatus operating at 100 rpm.

Initially the following solution is prepared: 40.8 g KH_2PO_4 is dissolved in 1500 ml of water. pH is adjusted to 7.2 with NaOH (40%) and 4500 ml of water is added.

The tablet/capsule to be tested is added to 1000 ml medium of 37°C prepared by diluting 150 ml 96% ethanol to 1000 ml with the above solution. After 3, 5, 10, 15, 30 and 60 minutes 10 ml samples are withdrawn and analyzed by UV spectrophotometry at 289 nm using medium as reference and a solution of 25 mg tolfenamic acid in 50.00 ml 0.1 N NaOH diluted 2 → 100 with medium as standard.

In Figure 2 dissolution curves for the tablet according to the invention and the prior art tablet and capsule formulations are shown. The much faster dissolution of the tablet according to the invention is evident.

In the preceding the invention has been described by means of specific examples of preferred embodiments. However it will be appreciated, that various modifications can be made by a person skilled in the art

without deviating from the spirit and scope of the invention.

PATENT CLAIMS

1. A tablet comprising an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof, said active ingredient having a mean particle size of ≤ 10 μm, and said tablet furthermore comprising alginic acid or a pharmaceutically acceptable salt thereof in an amount of 1.5 - 6.0 % by weight and a superdisintegrant in an amount of at least 6 % by weight.

2. A tablet according to claim 1, wherein the superdisintegrant is selected from cross-linked polyvinylpyrrolidones, particularly crospovidone, modified starches, particularly sodium starch glycolate, Starch 1500, croscarmellose sodium, LHPC (Low substituted hydroxypropylcellulose) and Veegum.

3. A tablet according to claim 1 or 2, wherein the superdisintegrant is present in an amount of at least 8 % by weight, particularly in an amount of at least 10 % by weight and preferably in an amount of at least 12 % by weight.

4. A tablet according to one or more of the preceding claims, wherein the superdisintegrant is present as an extragranular disintegration agent.

5. A tablet according to one or more of the preceding claims, wherein the superdisintegrant is present both as an intragranular disintegration agent and as an extragranular disintegration agent.

6. A tablet according to one or more of the preceding claims, wherein the alginic acid or the pharmaceutically acceptable salt thereof is included as a granulation agent.

7. A tablet according to one or more of the preceding claims, wherein the particle size of the active ingredient has been provided by milling or micronizing.

8. A tablet according to one or more of the preceding claims, wherein the specific surface area of the active ingredient is in the range from 1.0 - 4.0 m^2/cm^3.

9. A tablet according to one or more of the preceding claims comprising from 40 - 70 % by weight of the active ingredient, from 2.5 - 5.0 % by weight of alginic acid or a pharmaceutically acceptable salt thereof, from 6 - 10 % by weight of intragranular sodium starch glycolate, from 3 - 5 % by weight of extragranular sodium starch glycolate and from 1 - 3 % by weight of extragranular croscarmellose sodium, the remainder up to 100 % by weight consisting of conventional tablet formulation aids, such as fillers, binding agents, disintegrants, lubricants, etc.

10. A tablet according to one or more of the preceding claims comprising a unit dose of tolfenamic acid or a pharmaceutically acceptable salt thereof, of about 200 mg tolfenamic acid, or a multiple of such unit doses, and having a total weight of 350 - 400 mg per unit dose, preferably about 375 mg per unit dose.

11. A tablet according to one or more of the preceding claims being capable of providing a mean plasma concentration of tolfenamic acid of about 2.00 µg/ml within half an hour after administration.

12. A method of preparing a tablet according to one or more of the preceding claims, comprising the following steps:

a) blending an active ingredient selected from tolfenamic acid and pharmaceutically acceptable salts thereof having a mean particle size of ≤ 10 µm with a disintegration agent and optionally other intragranular tablet formulation aids,

b) kneading the resulting blend with a solution or dispersion of alginic acid or a pharmaceutically

acceptable salt thereof to form a moist homogeneous mass, the alginic acid or pharmaceutically acceptable salt thereof being used in an amount to give a concentration thereof in the resulting tablet of 1.5 - 6.0 % by weight, and granulating the moist homogeneous mass,

c) drying the obtained granules, optionally after blending with a filler and/or other tablet formulation aids,

d) blending the dried granules with a disintegration agent and optionally other extragranular tablet formulation aids, and

e) compressing the resulting blend into a tablet,

with the proviso that the disintegration agent used in step a) and/or step d) comprises one or more superdisintegrants in a total amount to give a concentration of superdisintegrant in the resulting tablet of at least 6 % by weight.

13. The use of tolfenamic acid or a pharmaceutically acceptable salt thereof having a mean particle size of ≤ 10 μm in combination with alginic acid or a pharmaceutically acceptable salt thereof and a superdisintegrant for the preparation of a tablet for treatment of pain, inflammation, migraine, dysmenorrhoea and fever, particularly for acute treatment thereof, the alginic acid or pharmaceutically acceptable salt thereof and the superdisintegrant being used in amounts of 1.5 - 6.0 % by weight and at least 6 % by weight, respectively.

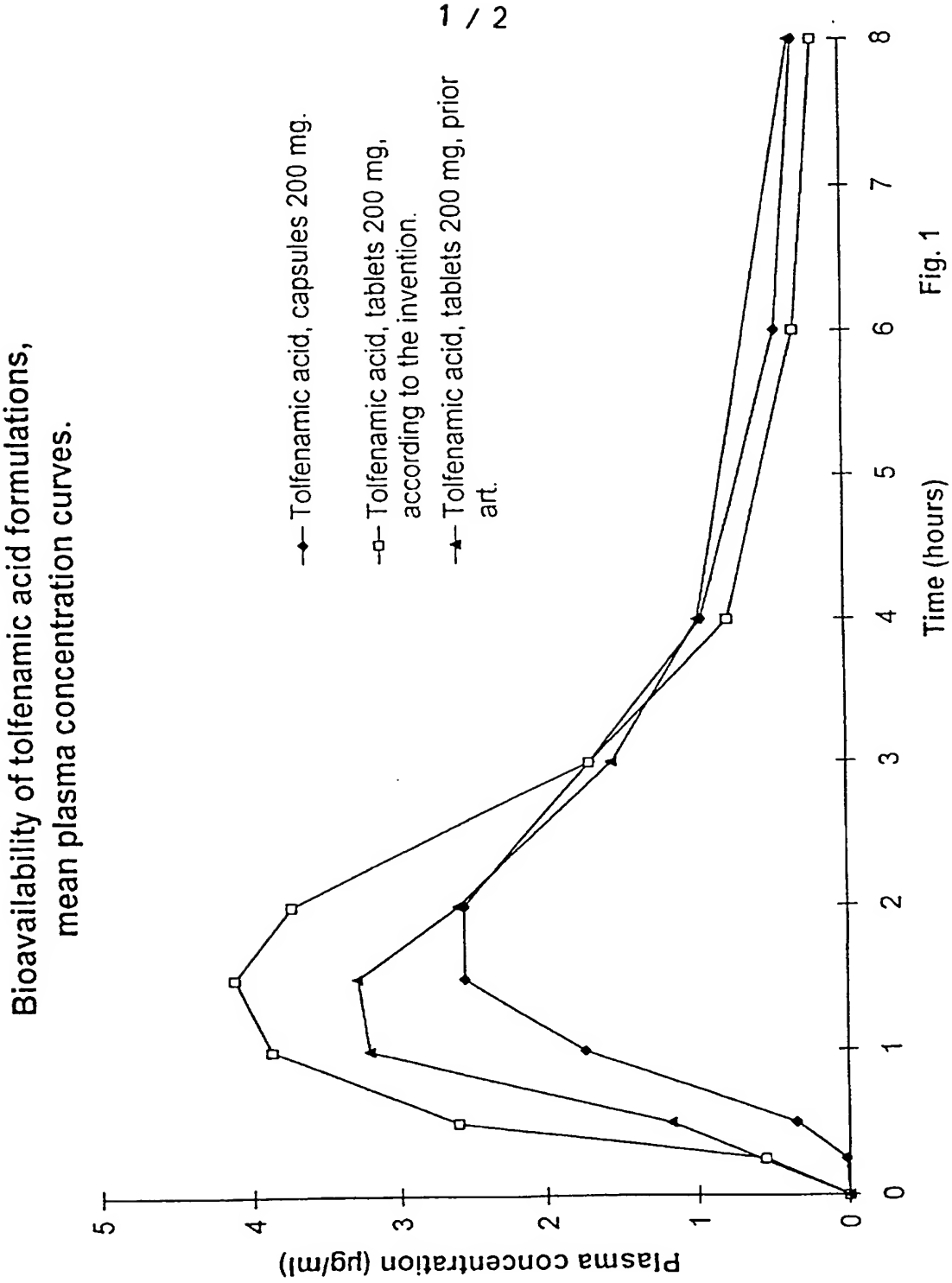
Bioavailability of tolfenamic acid formulations,
mean plasma concentration curves.
Tolfenamic acid, capsules 200 mg.
Tolfenamic acid, tablets 200 mg, according to the invention.
Tolfenamic acid, tablets 200 mg, prior art.
Plasma concentration (µg/ml)
Time (hours)
0
1
2
3
4
5
6
7
8

Fig. 1

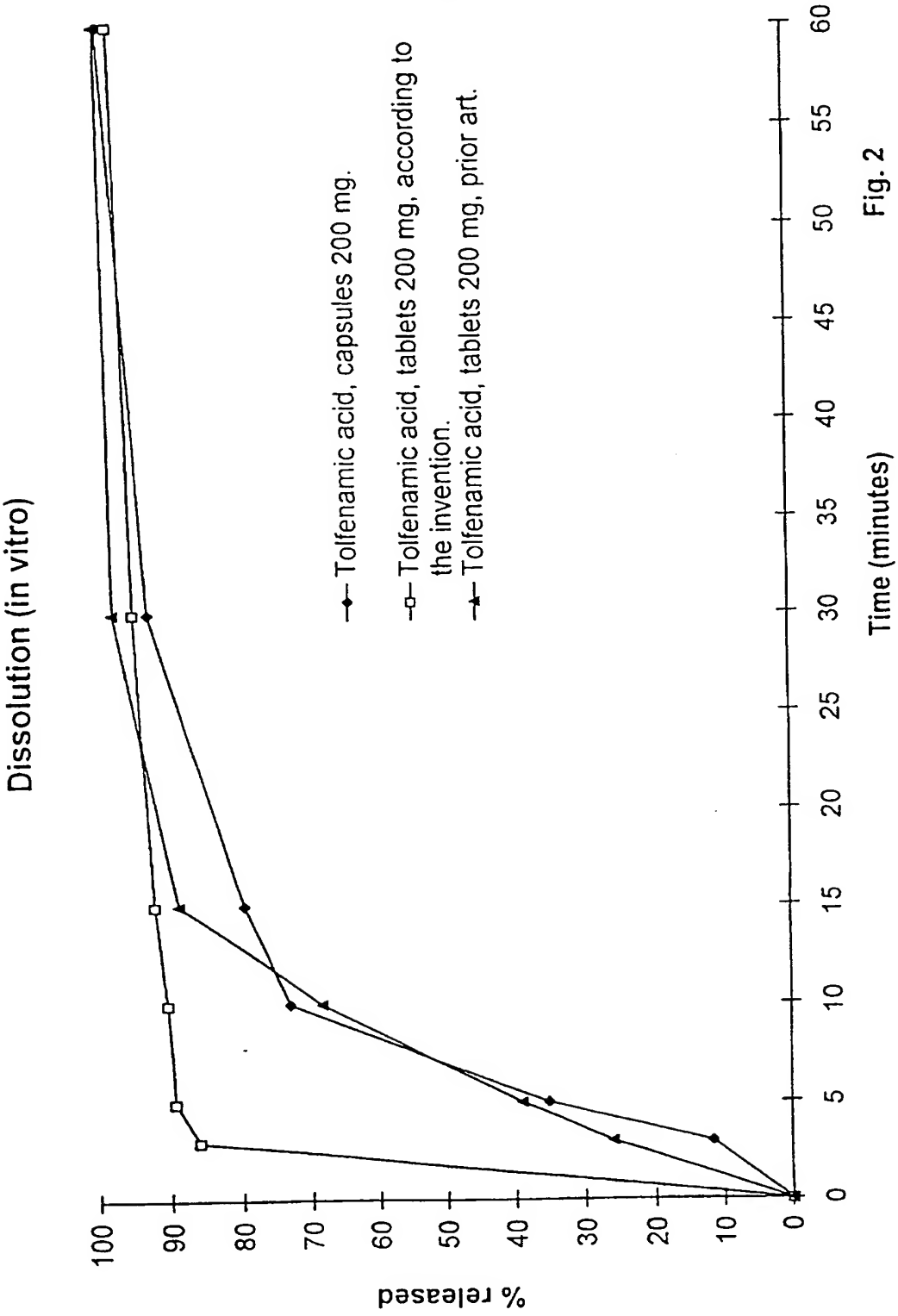
Dissolution (in vitro)
% released
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (minutes)
Tolfenamic acid, capsules 200 mg.
Tolfenamic acid, tablets 200 mg, according to the invention.
Tolfenamic acid, tablets 200 mg, prior art.

Fig. 2

INTERNATIONAL SEARCH REPORT

Inter ..onal Application No
PCT/DK 96/00548

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195 A61K9/20 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 41617 A (APPLIED PHARMA RES ;CONTE UBALDO (IT); MAGGI LAURETTA (IT); REINER) 27 December 1996 see page 5, line 30-32 see page 6, line 9-15 see page 7, line 12 see claim 23	1-13
X	WO 89 07439 A (NEUVONEN PERTTI J) 24 August 1989 see page 3, line 27 see page 6; example 1	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 1997	06.05.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Herrera, S

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 96/00548

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